See also, page 4, lines 18-23 and page 15, line 11- page 16, line 21. As these passages and the rest of the specification make clear, AP-1 and ER proteins are considered separately from the relevant cognate nuclear receptor. Accordingly, the amendments introduce no new matter.

THE CLAIMS, AS AMENDED, ARE CLEAR

Claims 1, 11 and 12- 13 were rejected under 35 U.S.C. §112, second paragraph, and claim 6 was objected to for improper punctuation. Applicants have amended the claims as helpfully suggested by the Examiner, overcoming the rejection. To the extent that the rejections are maintained against the amended claims, Applicants respectfully traverse as noted below.

The punctuation of claim 6 has been amended to delete a duplicate period, as helpfully suggested by the Examiner.

Claim 11 has been amended to delete extraneous language relating to AP-1 and Fos. Claim 11 was rejected under both 35 USC §112 first and second paragraph; both rejections are overcome by the correction to the claim.

Claims 12 and 13 have been corrected with respect to antecedence, to indicate "nuclear transcription factor ligand" rather than "nuclear transcription factor," correcting term reference with respect to claim 1, as helpfully suggested by the Examiner.

Claim 1 has been amended to specifically proviso ER, AP-1 and its constituents (fos and jun) out of the relevant claim element. Accordingly, any possible interpretation of the term "nuclear transcription factor ligand" or "cognate receptor" in the claim that includes these components is moot. With respect to the argument that the term is not clear in not reciting a structural or functional definition of the term, Applicants note that the passage in the specification helpfully cited by the Examiner indicates that nuclear transcription factors "are capable of entering the nucleus of a cell and, once there, effecting the up-regulation or down-regulation of one or more genes." Page 5, line 31- page 6, line 1. Accordingly, the term is defined with respect to function. Applicants believe that the definition of the term is reasonably clear and that the Examiner's concerns with respect to inclusion of ER, AP-1, fos or jun in the claim element have been completely addressed by the presented amendment. Accordingly, Applicants respectfully submit that the rejection should be withdrawn.

THE CLAIMS MEET THE REQUIREMENTS OF WRITTEN DESCRIPTION

Claims 1-5 and 8-11 were rejected for lack of written description. Applicants respectfully traverse this rejection, to the extent that it may be applied to the amended claims.

The rejection urges that the genus of ligands and cognate receptors is not structurally or functionally defined, and thus, that the claim relates to subject matter that inventors were not in possession of at the time of filing. Applicants respectfully disagree.

As an initial matter, the components of the method at issue have a clear functional characterization. As defined in the specification, the relevant receptors "are capable of entering the nucleus of a cell and once there, effecting the up-regulation or down regulation of one or more genes. A 'nuclear transcription factor ligand' is a compound that binds to a nuclear transcription factor." Specification, starting at page 5, line 31. Accordingly, the genus of the receptors and ligands at issue is quite clearly defined by function.

Moreover, as the Federal Circuit has most recently indicated, the issue when evaluating written description is not the complete description of a genus (structurally or functionally), or even "possession" of the invention. Instead, the issue that "the language of the specification...must describe the claimed invention so that one skilled in the art can recognize what is claimed." Enzo Biochem, Inc. v. Gen-Probe Incorporated. ____ F.3d ____. (Fed. Cir. July 15, 2002; 01-1230). Structural and functional descriptions of claim elements are simply ways of assisting one of skill in recognizing what is claimed. Put another way, one skilled in the art, reading the original disclosure, must reasonably discern the limitation at issue in the claims. Waldemar Link GmbH & Co. v. Osteonics Corp., 31 USPQ2d 1855, 1857 (Fed. Cir. 1994). *See also,* Union Oil Co. of California v. Atlantic Richfield Co., 54 USPQ2d 1227 (CAFC 2000): the "written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" *Id.* at 1232 (citation omitted).

In essence, the rejection's central argument is that the cognate receptor is not structurally defined (as noted above, the relevant components are, in fact, functionally defined) and that, therefore, one of skill could not envision the structure of the receptor and, therefore, could not describe the structural genus of receptors. The basic problem with this analysis is that the claimed invention is a method of screening nuclear transcription factor ligands and cognate receptors for the ability to modulate estrogen activation at an AP-1 site. Any nuclear transcription factor ligand and

cognate receptor, regardless of structure, can be screened in the assay. Thus, the structure of either component is simply not relevant to the claimed method. As set forth above, the issue for written description is simply whether the screening method (and not the materials to be screened by the method) is claimed in such a way that "one of skill in the art can recognize what is being claimed." The claim manifestly meets this test for written description because one of skill can easily determine whether the steps of the method are being practiced by reference to the steps and the definitions of the components at issue, regardless of the structure of the ligand and receptor screened in the method. Accordingly, the rejection should be withdrawn.

THE CLAIMS ARE ENABLED

The claims were additionally rejected for alleged lack of enablement. The rejection argues that the claims are enabled for functional receptors, but not for various non-functional receptors. Applicants respectfully traverse.

As noted above, the relevant receptors, by definition, "are capable of entering the nucleus of a cell and once there, effecting the up-regulation or down regulation of one or more genes. A 'nuclear transcription factor ligand' is a compound that binds to a nuclear transcription factor." Accordingly, the claims do not actually read on the use of non-functional receptors, as argued.

Moreover, even if the claims did read on such non-functional receptors, it would not render the claims non-enabled. Specifically, whether active or not, receptors and their ligands can be tested for AP-1 mediated estrogenic activity by the methods of the invention. Functional receptors may or may not have AP-1 mediated activity. Non-functional receptors also may or may not have AP-1 mediated activity, depending, e.g., on why they are non-functional (and in what context one considers functionality). Regardless, there simply is no difference in how the receptors (functional or non-functional) are used in the methods.

The rejection also urges that the claims read on the use of orphan receptors in the method. Here again, whether the claim reads on orphaned receptors or not, the method is practiced in exactly the same way. One of skill need undertake no experimentation whatsoever to practice the claimed method, whatever experimentation is required to identify a ligand for an orphan receptor. Orphan receptor ligand identification is not a feature of the claimed invention. In this regard, the Examiner is respectfully reminded that rejections for undue breadth/lack of enablement relating to

noninventive aspects of a claim are improper. *See,* e.g., In re Herschler 200 USPQ 711 (CCPA 1979). In Herschler, the claims were directed to the use of dimethyl sulfoxide (DMSO) to enhance tissue penetration of physiologically active steroidal agents. The claims were directed to the delivery of all physiologically active steroids while the specification provided only a single example demonstrating the efficacy of the delivery methods. The court reversed the Patent Office's rejection of these claims reasoning that, because the invention was not the discovery of novel steroidal agents but the delivery of steroidal agents in combination with DMSO, demonstration of the efficacy of the invention with a number of steroidal agents was not required under §112, first paragraph. Similarly, the claimed invention is a universally applicable screening method to test receptors and their ligands for AP-1 mediated estrogen activation, and not the discovery of orphan receptor ligands. Accordingly, the rejection should be withdrawn.

THE CLAIMS ARE NOT ANTICIPATED

Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,723,291 (Kushner *et al.*). Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Gaub *et al.* (1990) *Cell,* 63: 1267-1276. Claims 1-5, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 5,639,592 (Evans *et al.*). Claims 1-2, 4, 8, and 10-11 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,004,748 (Pfahl *et al.*). Applicants respectfully traverse.

In general, the rejections are overcome by the amendments to claim 1 which clarify that the cognate receptor is not ER, AP1, fos or jun. All of the art cited for anticipation purposes relies on an interpretation of the cognate receptor as being either an ER, AP1, fos or jun. In the interests of expediting prosecution, the claims have been amended to render this issue moot. Accordingly, the rejections are overcome by the amendments to the claims and the rejections must be withdrawn. Further analysis is provided below.

U.S. Patent 5,723,291 (Kushner *et al.*).

The claims require, *inter alia*:

"providing a first cell comprising: an estrogen receptor; a cognate receptor for said nuclear transcription factor ligand, wherein said cognate receptor is a receptor other than the estrogen receptor, AP-1, fos or jun; fos; jun; and, a promoter comprising an AP-1 site that regulates expression of a first reporter gene."

The rejection has not established where the 5,723,291 patent discloses a screening method in which a cell containing a cognate receptor (other than ER or AP-1) for a nuclear transcription factor ligand is contacted with the ligand for the cognate receptor. The rejection's citation of AP-1 (or fos or jun) as the cognate receptor are, therefore, clearly overcome by the amendment to claim 1.

The rejection's citation of columns 10, 13 and figures 10-12 are also believed moot, as the compounds being tested relate to activity mediated by ER (which was discovered in the '291 patent to be a transcription factor for AP1, as well as for classical EREs). ER is also provisoed out of claim 1 with respect to what constitutes the cognate receptor, thereby clarifying the claim to overcome the issues noted by the rejection.

Because Kushner et al. do not teach the elements of claim 1, the reference does not anticipate the claims and the rejection must be withdrawn.

Gaub *et al.* (1990) *Cell*, 63: 1267-1276.

Gaub *et al.* also fails to anticipate the presently claimed invention. The rejection urges that claim 1 prior to amendment could have been interpreted as having multiple molecules of fos or jun, some of which are read as meeting the fos or jun limitation of the claim and some of which are read as reading on the cognate receptor limitation. To facilitate prosecution, Applicants have amended the claim to make it as clear as possible that the cognate receptor is something other than fos or jun, rather than just another molecule of fos or jun. As neither jun nor fos are cognate receptors for the nuclear transcription factor ligand in the claim, the Gaub *et al.* reference fails to disclose a cell comprising both an estrogen receptor and a cognate receptor for a transcription factor ligand. The claims, therefore, clearly are not anticipated by Gaub *et al.* Accordingly, the rejection must be withdrawn.

U.S. Patent 5,639,592 (Evans *et al.*).

The 5,639,592 patent also fails to disclose a method having all of the elements of the presently claimed methods. As explained above, particularly in view of their recitation as discrete elements and proviso from the definition of the cognate receptor, neither fos nor jun meets the relevant claim limitations. The '592 patent fails to disclose an assay method in which a cell is contacted with both a transcription factor ligand (which is not a fos or jun), and a compound having AP-1 mediated estrogenic activity. Accordingly, the rejection must be withdrawn.

U.S. Patent 6,004,748 (Pfahl *et al.*).

The 6,004,748 patent also fails to anticipate the presently pending claims. As explained above, particularly in view of the claim amendments, neither fos nor jun meets the relevant claim element limitations. The '748 patent fails to disclose a method that involves contacting a cell with a compound having AP-1 mediated estrogenic activity (*e.g.* β-estradiol), with a transcription factor ligand (which is not ER, fos or jun). Lacking such a teaching, the '748 patent fails to anticipate the claims are issue. The rejection must be withdrawn.

THE CLAIMS ARE NOT OBVIOUS

Claims 1-13 were rejected for alleged obviousness over Kushner in view of various secondary references. Applicants respectfully traverse.

Applicants note that the present application is a CPA, filed December 26, 2001. Applicants further note that Kushner and the subject application were under a common obligation of assignment at the time the invention was made. Accordingly, Kushner is not prior art under section 103. The Examiner's attention is specifically drawn to 35 USC § 103 (c). Accordingly, the rejection is premised upon combination of a primary reference which is not available as prior art with various secondary references.

Moreover, even if Kushner were available as prior art for obviousness, which it is not, nothing in the rejection establishes how the references in combination meet the limitations of the amended claims, e.g., for essentially the reasons noted above. Therefore, the rejection must be withdrawn.

DOUBLE PATENTING

Claims 1-13 were rejected for alleged obviousness-type double patenting over claims 1-27 of 5,723,291 in view of various secondary references. Applicants respectfully traverse.

As with the anticipation and obviousness rejections noted above, the double patenting rejection is premised upon an argument that the cognate receptor is AP1, or fos or jun. For the reasons noted above, this issue is overcome by amendment.

With respect to the argument that one would have taken various methods relating to glucocorticoid receptor, retinoic acid receptors and the like and combined these teachings with the claims of the '291 application, Applicants respectfully disagree. Without Applicant's fundamental discovery of the relationship between estrogen-mediated activation of AP1 sites and regulation of

those sites by nuclear transcription factors other than fos, jun or ER, no specific motivation can be drawn from the art providing any specific reason to combine the references as proposed. The rejection's general motivation for making the proposed combination is that one of skill would have been interested in understanding the regulatory effects of hormones and the like. Respectfully, this puts the cart before the horse. Specific motivation cannot be drawn from the fact that one of skill would have liked to have discovered the mechanism of action discovered by the Applicants and, once discovered, would have practiced Applicants' methods. The motivations which are drawn from the art must come out of the art itself and they must be specific for the combination at issue. They cannot be general motivation (e.g., a supposed urge to discover what might happen if references were combined in a manner that does not appear on the face of either reference) and they cannot derive from an interpretation of the art that takes the advantages provided by Applicants discovery as the motivation to discover the methods at issue. The Courts have repeatedly held that this sort of reconstruction is literally the clearest example of improper hindsight invention recreation that can be envisioned.

Accordingly, the rejection must be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. **APPLICANTS REQUEST AN EXAMINER INTERVIEW PRIOR TO ISSUANCE OF A FINAL OFFICE ACTION. THE EXAMINER IS REQUESTED TO CONTACT THE UNDERSIGNED TO ARRANGE AN APPROPRIATE TELEPHONIC INTERVIEW.**

More generally, if a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-7871.

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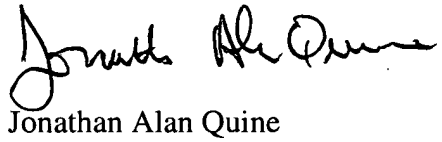
Respectfully submitted,



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APPENDIX A

"MARKED UP" CLAIMS ILLUSTRATING THE AMENDMENTS MADE TO THE CLAIMS OF 09/103,355 WITH ENTRY OF THIS AMENDMENT

1 (THREE TIMES AMENDED). A method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:

a) providing a first cell comprising:

an estrogen receptor;

a cognate receptor for said nuclear transcription factor ligand**, wherein said cognate receptor is a receptor other than the estrogen receptor, AP-1, fos or jun**;

fos;

jun; and,

a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and,

c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

2 (TWICE AMENDED). The method of claim 1, further comprising the steps of:

d) providing a cell **[containing]** **comprising** an estrogen receptor, a cognate receptor for said nuclear transcription factor ligand, and a promoter comprising an estrogen response element (ERE) that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

3 (AMENDED). The method of claim 2, wherein said first cell and the cell containing the estrogen response element that regulates expression of a second reporter gene are the same cell.

4 (TWICE AMENDED). The method of claim 1, further comprising the steps of:

d) providing a cell **[containing] comprising** a cognate receptor of said transcription factor ligand, and a promoter comprising a response element for said cognate receptor that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

5 (AMENDED). The method of claim 4, wherein said first cell and the cell containing a cognate receptor of said transcription factor ligand are the same cell.

6 (TWICE AMENDED). The method of claim 1, wherein said nuclear transcription factor ligand is selected from the group consisting of**:** a glucocorticoid, a progestin, vitamin D, retinoic acid, an androgen, a mineralcorticoid, and a prostangladin.**[.]**

7 (AMENDED). The method of claim 1, wherein said cognate receptor is selected from the group consisting of**:** an estrogen receptor, a glucocorticoid receptor, a progestin PR-A receptor, and progestin PR-B receptor, androgen receptor, a mineralcorticoid receptor, and a prostaglandin receptor.

8 (AMENDED). The method of claim 1, wherein said **first** cell expresses said estrogen receptor from a heterologous DNA.

9 (AMENDED). The method of claim 1, wherein said **first** cell expresses said cognate receptor from a heterologous DNA.

11 (TWICE AMENDED). The method of claim 10, wherein said **[AP-1 protein said fos or said]** jun is c-jun.

12 (TWICE AMENDED). The method of claim 1, wherein said nuclear transcription factor **ligand** is a progestin; and said cognate receptor is a progestin receptor.

13 (AMENDED). The method of claim 1, wherein said nuclear transcription factor **ligand** is a glucocorticoid and said cognate receptor is a GR receptor.

APPENDIX B

CLAIMS PENDING IN USSN 09/103,355 WITH ENTRY OF THIS AMENDMENT

1 (THREE TIMES AMENDED). A method of screening a nuclear transcription factor ligand for the ability to modulate estrogen activation at an AP-1 site, said method comprising the steps of:

a) providing a first cell comprising:

an estrogen receptor;

a cognate receptor for said nuclear transcription factor ligand**, wherein said cognate receptor is a receptor other than the estrogen receptor, AP-1, fos or jun**;

fos;

jun; and,

a promoter comprising an AP-1 site that regulates expression of a first reporter gene;

b) contacting said first cell with said transcription factor ligand and with a compound having AP-1 mediated estrogenic activity; and,

c) detecting expression of said first reporter gene, whereby an alteration in expression of said first reporter gene, as compared to expression of said first reporter gene in the absence of said transcription factor ligand, indicates that said nuclear transcription factor ligand modulates estrogen activation at an AP-1 site.

2 (TWICE AMENDED). The method of claim 1, further comprising the steps of:

d) providing a cell **comprising** an estrogen receptor, a cognate receptor for said nuclear transcription factor ligand, and a promoter comprising an estrogen response element (ERE) that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

3 (AMENDED). The method of claim 2, wherein said first cell and the cell containing the estrogen response element that regulates expression of a second reporter gene are the same cell.

4 (TWICE AMENDED). The method of claim 1, further comprising the steps of:

d) providing a cell **comprising** a cognate receptor of said transcription factor ligand, and a promoter comprising a response element for said cognate receptor that regulates expression of a second reporter gene;

e) contacting said cell with said transcription factor ligand and with said compound having AP-1 mediated estrogenic activity; and

f) detecting expression of said second reporter gene.

5 (AMENDED). The method of claim 4, wherein said first cell and the cell containing a cognate receptor of said transcription factor ligand are the same cell.

6 (TWICE AMENDED). The method of claim 1, wherein said nuclear transcription factor ligand is selected from the group consisting of**:** a glucocorticoid, a progestin, vitamin D, retinoic acid, an androgen, a mineralcorticoid, and a prostangladin.

7 (AMENDED). The method of claim 1, wherein said cognate receptor is selected from the group consisting of**:** an estrogen receptor, a glucocorticoid receptor, a progestin PR-A receptor, and progestin PR-B receptor, androgen receptor, a mineralcorticoid receptor, and a prostaglandin receptor.

8 (AMENDED). The method of claim 1, wherein said **first** cell expresses said estrogen receptor from a heterologous DNA.

9 (AMENDED). The method of claim 1, wherein said **first** cell expresses said cognate receptor from a heterologous DNA.

10 (AMENDED). The method of claim 1, wherein said cell expresses said fos or said jun from a heterologous DNA.

11 (TWICE AMENDED). The method of claim 10, wherein said jun is c-jun.

12 (TWICE AMENDED). The method of claim 1, wherein said nuclear transcription factor **ligand** is a progestin; and said cognate receptor is a progestin receptor.

13 (AMENDED). The method of claim 1, wherein said nuclear transcription factor **ligand** is a glucocorticoid and said cognate receptor is a GR receptor.